Clinical Trials and Clinical Practice: Surrogates at the Clinician/Patient Interface

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Outline

- Definitions & history
- Use in clinical practice
- Advantages & limitations
- Critical appraisal framework
Clinical scenario

- 67 year old, established ASHD
- Recent myocardial infarction
- LDL-C on target with a statin
- HDL-C below target
  - Well established as prognostic factor
  - Has not tolerated niacin
- Novel antilipemic agent recently marketed
  - Consistently increases HDL-C by up to 70%
  - No data on effect on clinical outcomes
  - Hailed as “a major therapeutic breakthrough”
  - “One of the most important compounds of our generation”
- Would you consider recommending this agent to your patient?
Definitions

- **Surrogate endpoint**
  - From Latin word *“subrogare”*
    - To substitute; to elect or ask in place of
  - “A laboratory or physical measurement that is used as a substitute for a clinically meaningful endpoint that is a *direct* measure of how a person:
    - Feels
    - Functions
    - Survives

Temple 1989
Definitions

- Biomarker
  - ‘A characteristic that provides an indication of:
    - Normal biologic processes
    - Pathogenic processes
    - Pharmacological responses
  - Biomarker ≠ surrogate endpoint
  - Surrogate endpoint ≠ biomarker
# Examples of surrogate endpoints

<table>
<thead>
<tr>
<th>Disease</th>
<th>Surrogate endpoint</th>
<th>Clinical endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sclerosis</td>
<td>MRI imaging of lesions</td>
<td>MS relapses</td>
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<tr>
<td></td>
<td></td>
<td>Disability progression</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>HDL-C</td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>Carotid intima-media thickness (CIMT)</td>
<td>Ischemic stroke</td>
</tr>
<tr>
<td>Diabetes</td>
<td>HgA1c</td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ischemic stroke</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Prostate-specific antigen (PSA)</td>
<td>Cancer-specific mortality</td>
</tr>
<tr>
<td></td>
<td>Distant metastasis</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>Tumour response</td>
<td>Cancer-specific mortality</td>
</tr>
<tr>
<td></td>
<td>Progression-free survival (PFS)</td>
<td>Overall survival</td>
</tr>
</tbody>
</table>
History

- 1980 – Biomarker
- 1988 – Surrogate marker
- 1989 – Surrogate endpoint
Applications in clinical practice

- Can be used for:
  - Diagnosis
  - Disease staging
  - Monitoring disease
  - Assessing response to therapy
Advantages

- Increase understanding of pathophysiology
- Identify novel therapeutic targets
- Enable clinical monitoring
- Reduce sample size & duration of trials
  - Reduced cost
  - Expedited access
  - Improved feasibility
Limitations

- ↓ power to detect harms
- Based on incomplete evidence
  - Underlying disease processes
  - Effects of intervention
- Surrogate failures
  - Excess morbidity & mortality
    - Human & economic cost
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MORTALITY AND MORBIDITY IN PATIENTS RECEIVING ENCAINIDE, FLECAINIDE, OR PLACEBO

The Cardiac Arrhythmia Suppression Trial


Abstract Background and Methods. In the Cardiac Arrhythmia Suppression Trial, designed to test the hypothesis that suppression of ventricular ectopy after a myocardial infarction reduces the incidence of sudden death, patients in whom ventricular ectopy could be suppressed with encainide, flecainide, or moricizine were randomly assigned to receive either active drug or placebo. The use of encainide and flecainide was discontinued because of excess mortality. We examined the mortality and morbidity after randomization to encainide or flecainide or their respective placebo.

Results. Of 1498 patients, 857 were assigned to receive encainide or its placebo (432 to active drug and 425 to placebo) and 641 were assigned to receive flecainide or its placebo (323 to active drug and 318 to receiving drug vs. 5 receiving placebo). Almost all cardiac deaths not due to arrhythmia were attributed to acute myocardial infarction with shock (11 patients receiving drug and 3 receiving placebo) or to chronic congestive heart failure (4 receiving drug and 2 receiving placebo). There were no differences between the patients receiving active drug and those receiving placebo in the incidence of nonlethal disqualifying ventricular tachycardia, proarrhythmia, syncope, need for a permanent pacemaker, congestive heart failure, recurrent myocardial infarction, angina, or need for coronary-artery bypass grafting or angioplasty.

Conclusions. There was an excess of deaths due to arrhythmia and deaths due to shock after acute recurrent myocardial infarction in patients treated with encainide or
CAST Trial – preliminary results

- Surrogate endpoint
  - Arrhythmia suppression:
    - 75% for encainide, flecainide or moricizine

Death from arrhythmia or cardiac arrest

![Graph showing patients without event over days after randomization for placebo and treated groups.]

- Treated = 4.5%
- Placebo = 1.2%
- RR = 3.6 (1.7-8.5)

Death from any cause

![Graph showing patients without event over days after randomization for placebo and treated groups.]

- Treated = 7.7%
- Placebo = 3.0%
- RR = 2.5 (1.6-4.5)

Figure 1. Actuarial Probabilities of Freedom from Death or Cardiac Arrest Due to Arrhythmia in 1498 Patients Receiving Encainide or Flecainide or Corresponding Placebo.

Figure 2. Actuarial Probabilities of Freedom from Death or Cardiac Arrest Due to Any Cause in 1498 Patients Receiving Encainide or Flecainide or Corresponding Placebo.

NEJM 1989;321:406-412
### Surrogate failures

<table>
<thead>
<tr>
<th>Year</th>
<th>Intervention</th>
<th>Surrogate</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>Milrinone</td>
<td>Exercise capacity&lt;br&gt;Left ventricular function</td>
<td>↑ mortality</td>
</tr>
<tr>
<td>1993</td>
<td>Flosequinan</td>
<td>Exercise capacity&lt;br&gt;Left ventricular function</td>
<td>↑ mortality</td>
</tr>
<tr>
<td>1993</td>
<td>Enalapril vs&lt;br&gt;Hydralazine + ISDN</td>
<td>Exercise capacity&lt;br&gt;Left ventricular function</td>
<td>Enalapril ↓ mortality&lt;br&gt;(contrary to surrogate findings)</td>
</tr>
<tr>
<td>1998</td>
<td>Vesnarinone</td>
<td>Exercise capacity&lt;br&gt;Left ventricular function</td>
<td>↑ mortality</td>
</tr>
<tr>
<td>2005</td>
<td>Fenofibrate</td>
<td>LDL-C</td>
<td>↔ Overall mortality</td>
</tr>
<tr>
<td>2008</td>
<td>Intensive glucose ↓</td>
<td>HgA1c</td>
<td>↑ mortality</td>
</tr>
</tbody>
</table>
# Surrogate failures

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<tbody>
<tr>
<td>2007</td>
<td>Torcetrapib †</td>
<td>HDL-C</td>
<td>↑ cardiovascular events ↑ mortality</td>
</tr>
<tr>
<td>2008</td>
<td>Ezetimibe (add on)</td>
<td>LDL-C</td>
<td>↔ carotid IMT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carotid IMT</td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>Androgen deprivation</td>
<td>Distant metastasis</td>
<td>↑ CVD mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prostate cancer mortality</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>Fenofibrate (add on)</td>
<td>LDL-C</td>
<td>↔ overall mortality</td>
</tr>
<tr>
<td>2010</td>
<td>Bevacizumab</td>
<td>Disease-free progression</td>
<td>↔ overall mortality</td>
</tr>
<tr>
<td>2011</td>
<td>Niacin ER (add on)</td>
<td>HDL-C</td>
<td>↔ cardiovascular events ↑ ischemic stroke</td>
</tr>
</tbody>
</table>

† Findings published before torcetrapib was approved for use by the FDA
Validity assessment

- Epidemiology
  - Important but imperfect science
    - Measures ‘associations’ not ‘causation’
    - “A perfect correlate does not a surrogate make”
      (Baker & Kramer 2003)

- Framework needed for determining the validity of the surrogate endpoint
Critical appraisal framework

- Surrogate-clinical outcome relationship causal?
  - Biological plausibility
  - Strong association
  - Independent association
  - Consistent association
    - Across studies
    - Across drug classes
    - Drugs within same class
  - Evidence of dose-response
Critical appraisal framework

- Effect of intervention on surrogate consistent with its effect on clinical outcome?
  - Study with both endpoints
  - Ideally RCT evidence

- Intervention mediates all of its impact via the surrogate
  - Within a drug class
  - Across drug classes of similar action

- Unintended adverse effect?
Clinical scenario

- Torcetrapib
- Efficacy tested in two RCT of patients at high risk of coronary events
- Endpoints
  - HDL-C
  - Progression of coronary atherosclerosis
  - Carotid IMT
  - Cardiovascular events
  - All-cause mortality
- Results
  - Increased risk of cardiovascular events and all-cause mortality
Conclusions

- Role of surrogate endpoints
  - Advancing our understanding of disease
  - Identifying novel therapeutic targets
  - Indispensable in early phases of drug development
  - Not for drug approval ... some exceptions

- In clinical practice
  - Evaluate using critical appraisal framework
Skating on thin ice